

Demystifying Medicine Lecture Series

Obesity: Brown and Other Fat

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Conflict of Interest Disclosure

Aaron M. Cypess

The medication mirabegron (Myrbetriq®, Astellas Pharma) will be described in the context of trying to activate human brown adipose tissue and energy expenditure by using a dose of 200 mg, which is higher than the FDA's highest-approved dosage of 50 mg for treating overactive bladder.

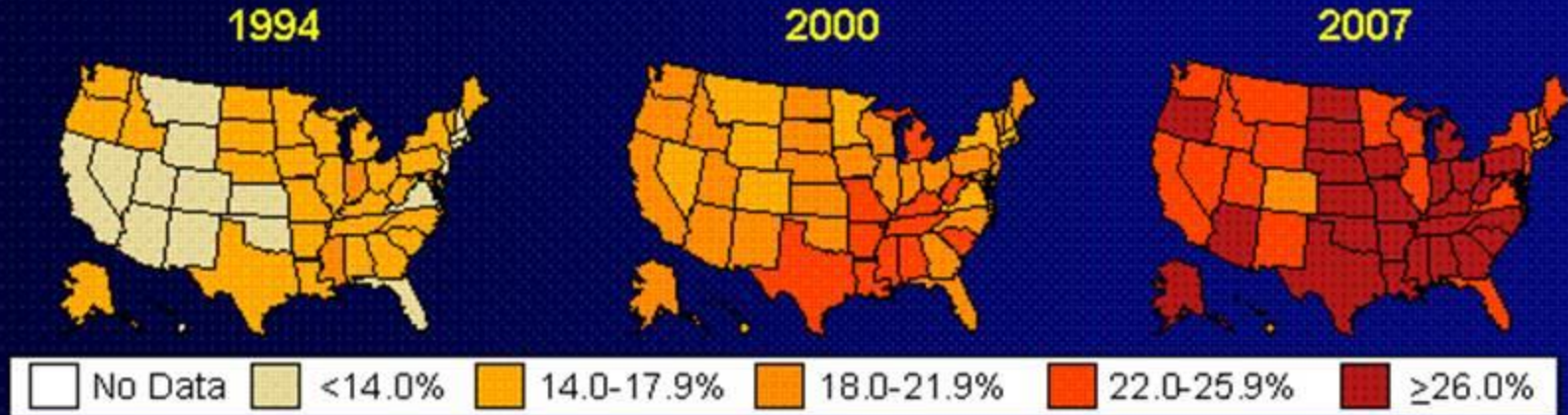
I have no relationship with Astellas Pharma.

Objectives

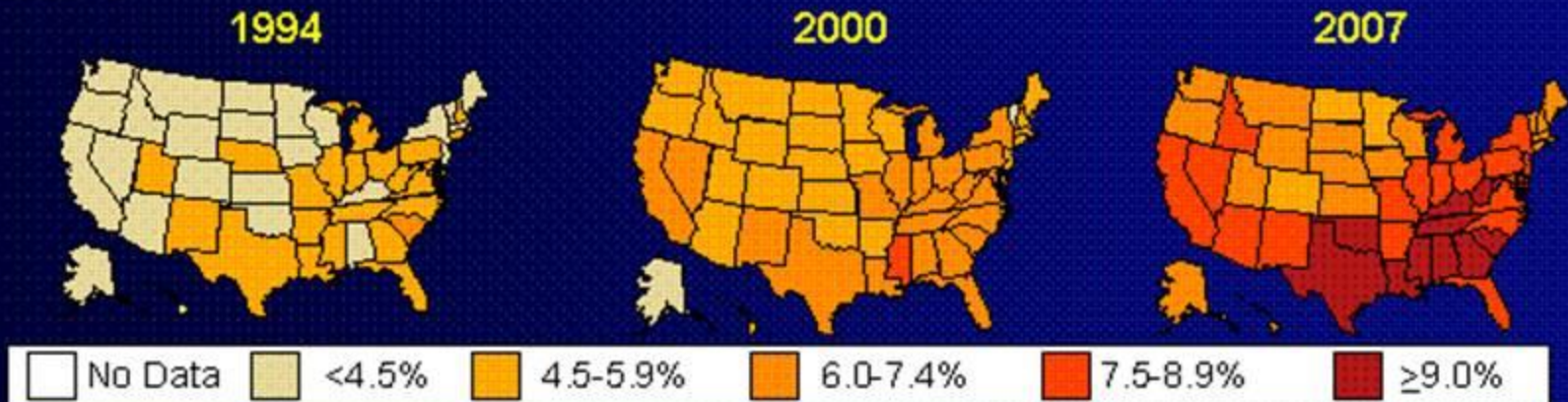
1. Distinguish the structural and functional differences between brown and white adipose tissue.
2. Identify which imaging modalities are available to study brown fat function.
3. List the interventions already shown to increase brown adipose tissue mass and activity.
4. Based on the currently available data, describe the likelihood that brown adipose tissue will be a treatment target for obesity and diabetes.

Too Much Fat is Highly Morbid

Obesity (BMI ≥ 30 kg/m²)



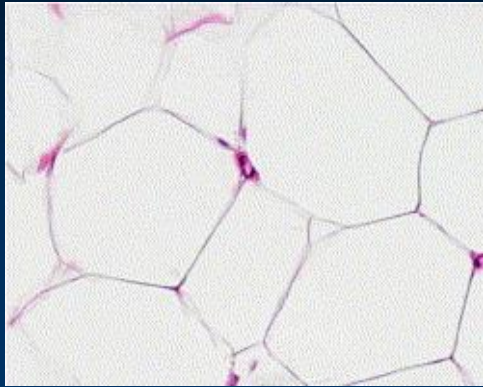
Diabetes



CDC's Division of Diabetes Translation. National Diabetes Surveillance System available at <http://www.cdc.gov/diabetes/statistics>

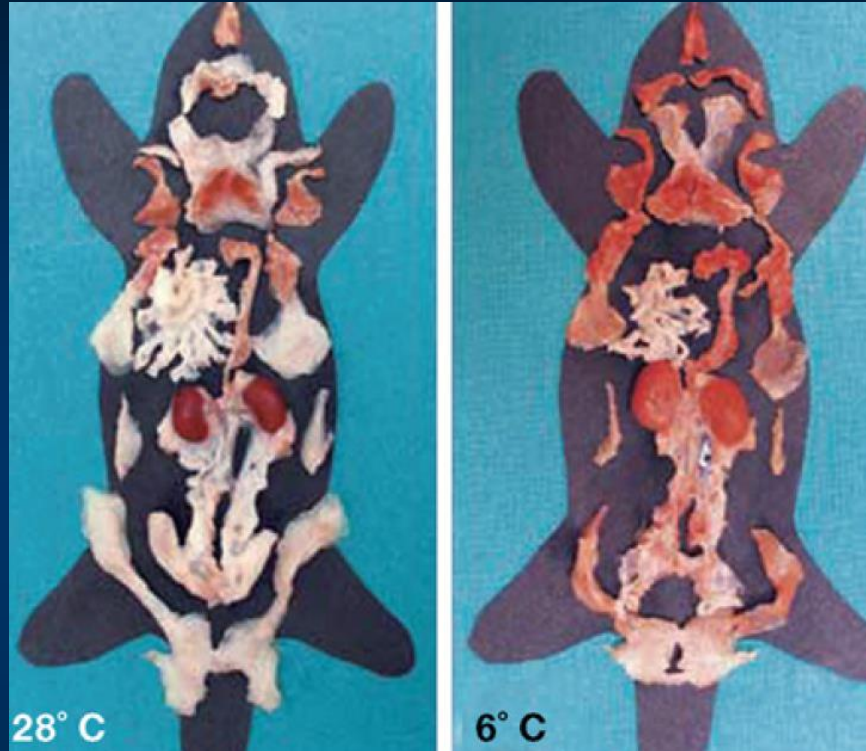
At Least Two Types of Fat

White (WAT)



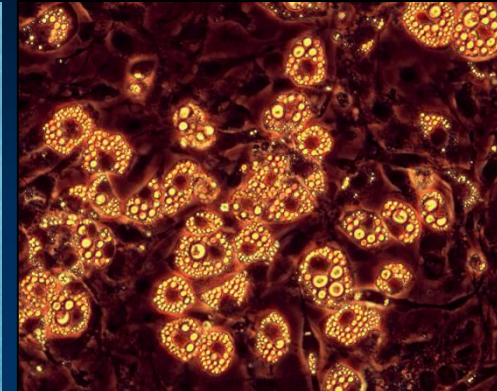
***Energy
storage***

50g contains
300-500 kcal



- ❖ Cold-induced [NST]
- ❖ Diet-induced [DIT]

Brown (BAT)



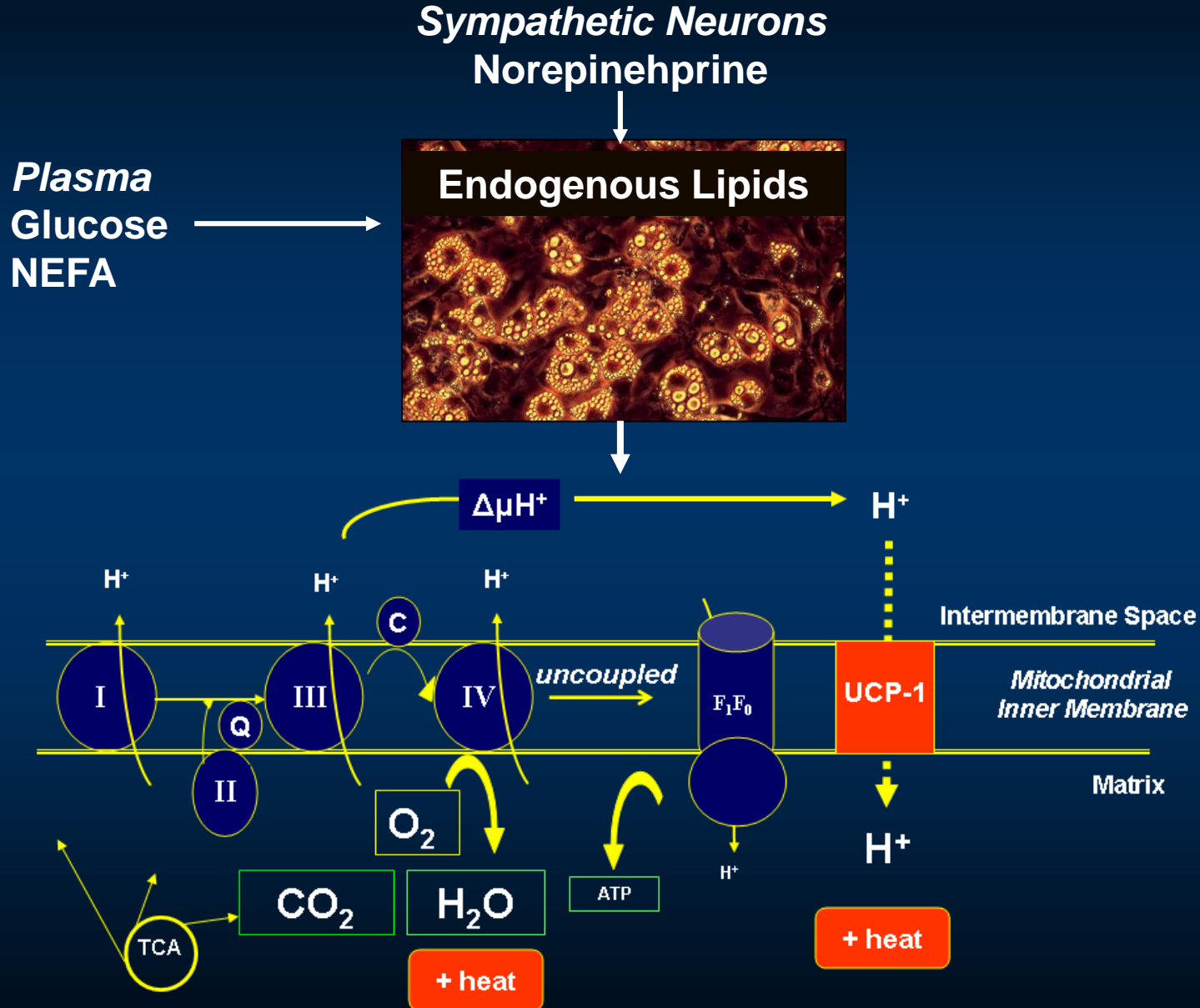
Energy

expenditure

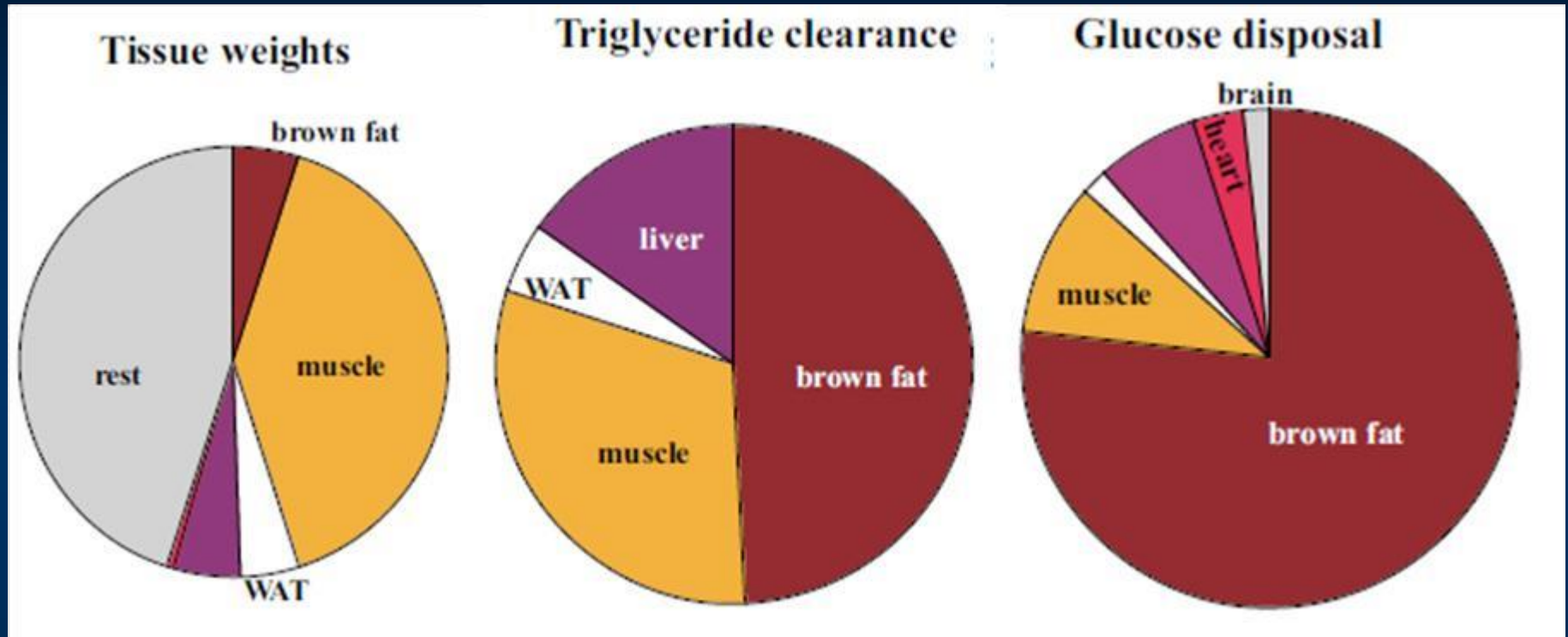
50g consumes
100-300 kcal/d ?

**Uncoupling Protein-1
[UCP1]
Thermogenesis**

A. How Brown Fat Consumes Fuel to Generate Heat



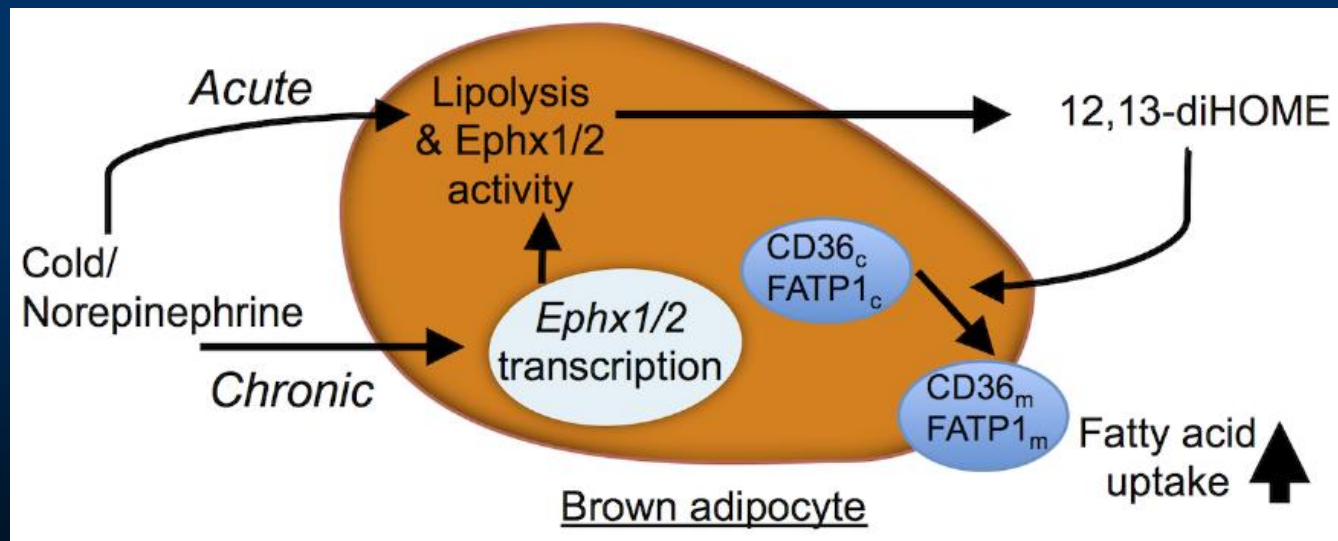
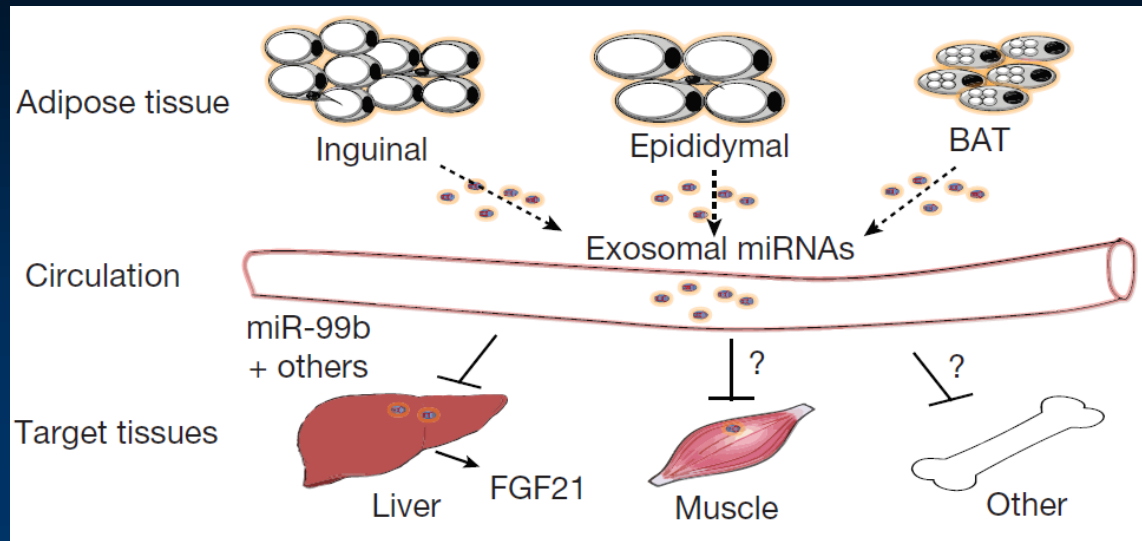
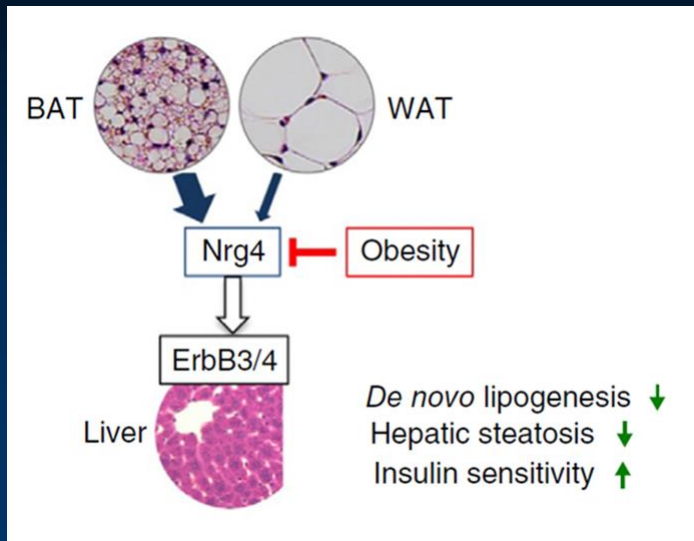
B. Brown Fat May be Used for Treating Metabolic Dysregulation



- BAT in cold-acclimatized mice consumes more than half of ingested lipids and glucose.

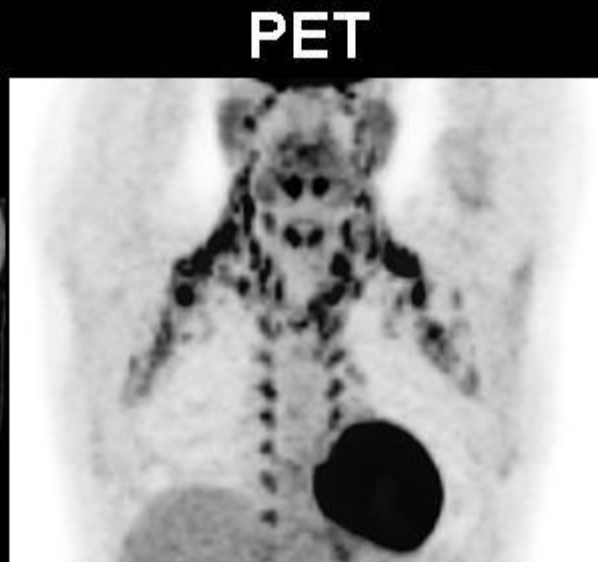
Bartelt A...Heeren J Nat Med. 2011;17:200-5; Nedergaard J & Cannon B. Cell Metab. 2011;13:238-40.

C. Endocrine Roles for Brown Adipose Tissue



Circa 2002: Adults Humans Have FDG-Avid Adipose Tissue = F-A-A-T

- CT = Computed Tomography → structure
- PET = Positron Emission Tomography (^{18}F FDG) → function
- PET/CT = metabolic activity of each tissue



The Challenge, circa 2006

“You believe that there is no significant brown fat in adult humans and that what we see on PET/CT is not brown fat?”

-Cypess

**“Yes, that's pretty much it....
I would be very surprised if those PET images were brown fat deposits.”**

-KOL Endocrinologist

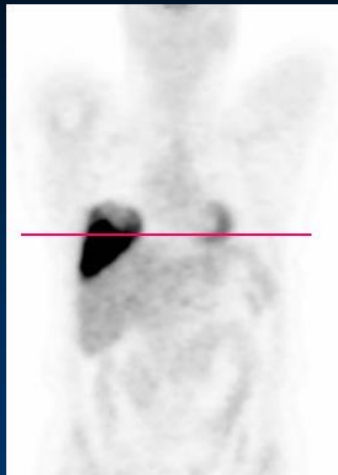
“In FDG-PET scans, you very often see false positive signals from brown fat....How do we know that it's brown fat?”

-Cypess

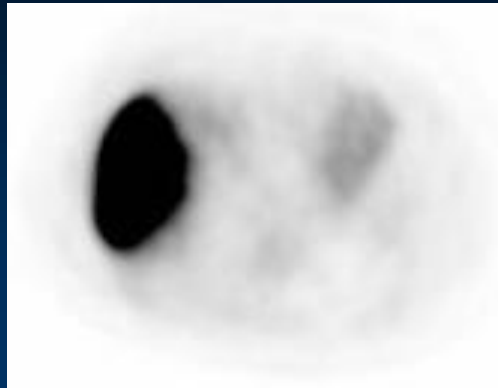
“Because everyone says so!”

-A Professor of Radiology

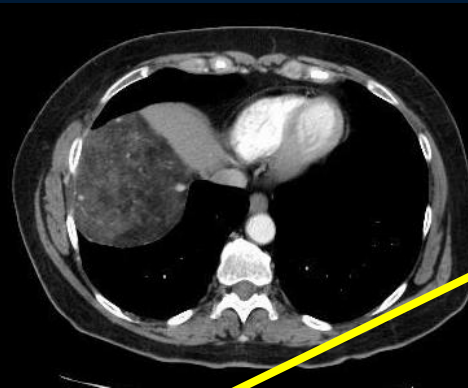
UCP1+ Benign Brown Fat Mass



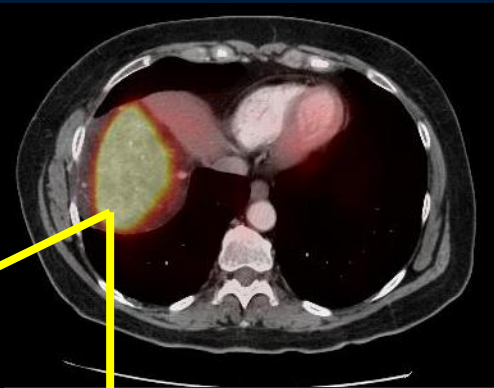
PET



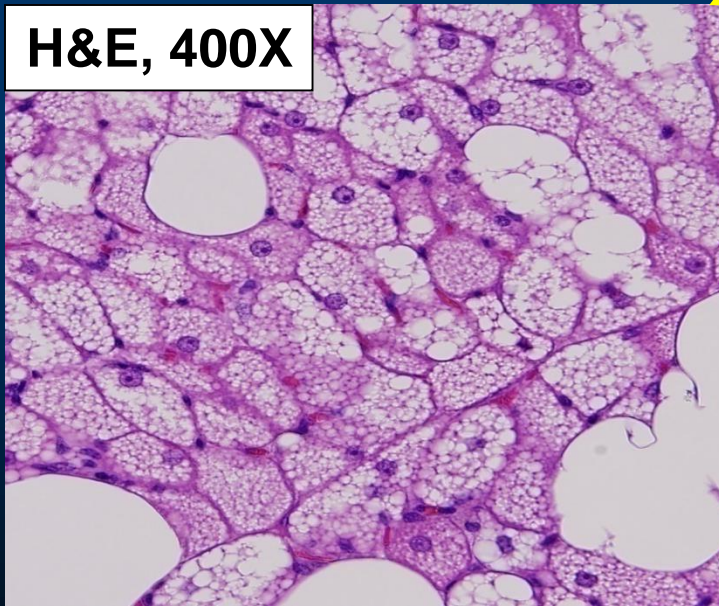
CT



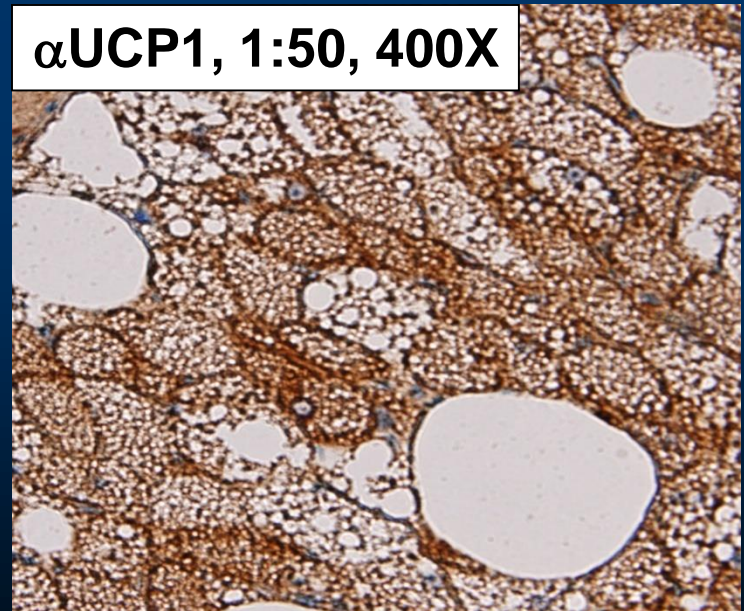
PET/CT



H&E, 400X



α UCP1, 1:50, 400X



The Initial Understanding of Human Brown Fat

Structure

- Predominantly in specific regions of the body.
- We can measure it non-invasively via PET/CT.

Function

- Protects against cold acutely [NST].
- People with detectable brown fat are more frequently female, younger, leaner [DIT?], and not taking beta-blockers.
- **Nearly every adult human has brown fat.**

The Next Questions

- A. To what extent does adult human BAT contribute to increased energy expenditure?**
- B. How does BAT's uptake of plasma glucose and triglycerides impact whole-body fuel metabolism?**
- C. How does activated human BAT interact with other organs in regulating metabolism?**

Translational Approaches to Understanding BAT

Noninvasive Imaging

Mass and Activity

- PET/CT
- MRI
- Ultrasound

Integrative Physiology

Human, Rodent, in vitro

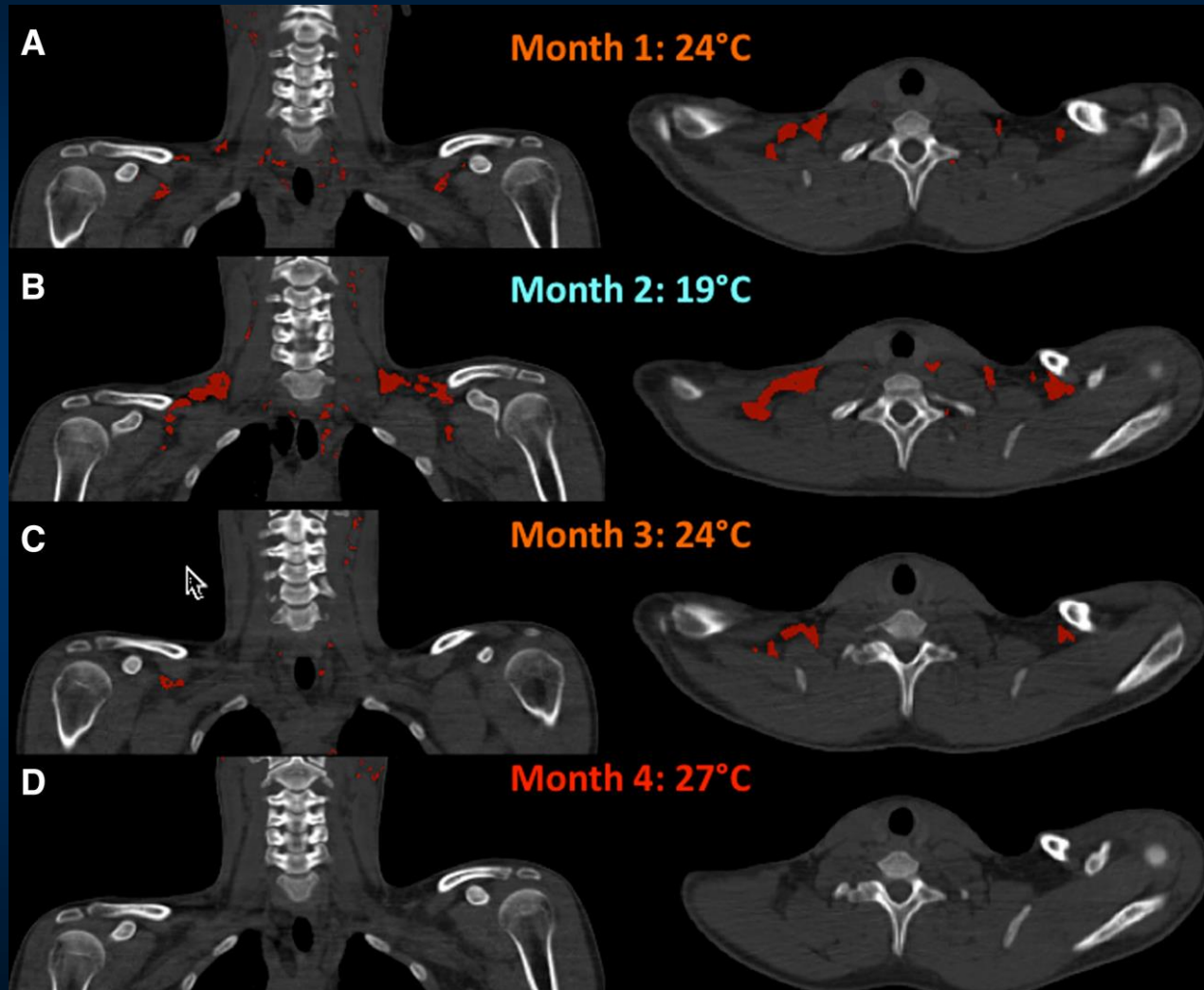
- Bioenergetics
- Proteomics
- Genomics

Therapeutics

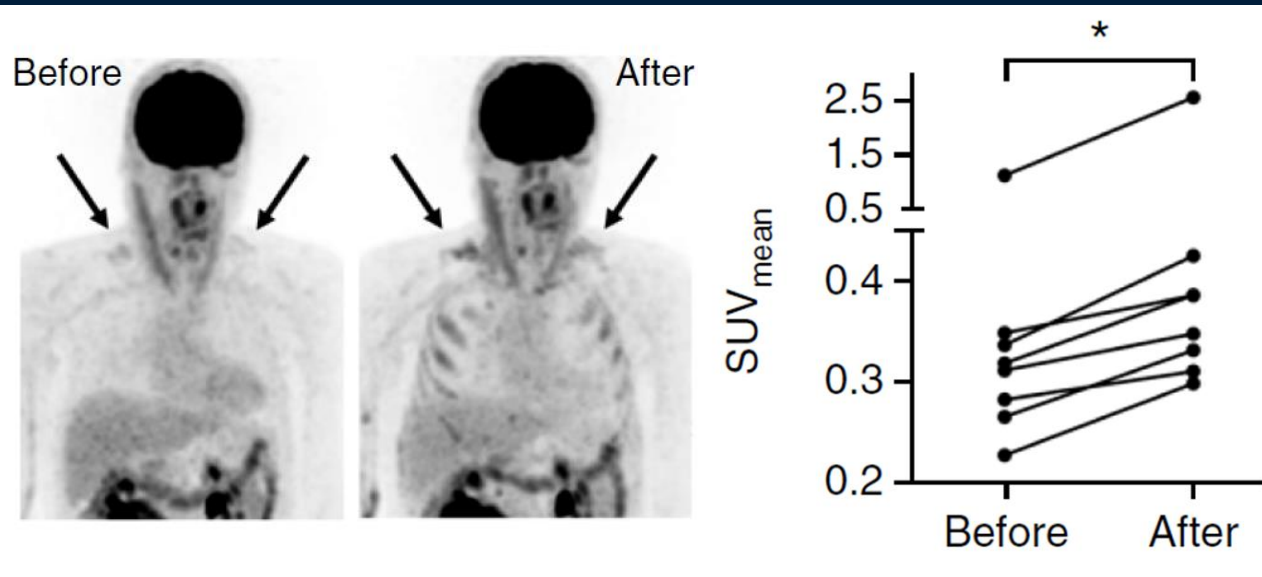
- Cold
- Rx/Hormone – β 3-ARA, etc.

BAT-based Therapeutics

Temperature can be used to increase – and then reduce – Human BAT activity



Cold Acclimation Improves Insulin Sensitivity in Patients with T2DM

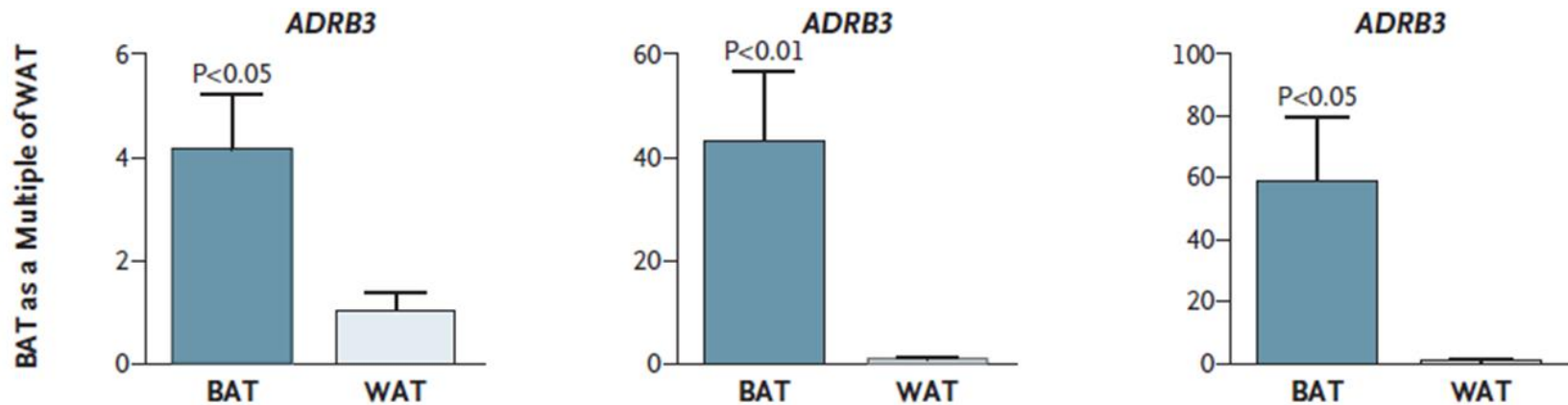


- In eight subjects with T2DM, ten days of cold acclimation (14–15 °C) increased BAT activity

Why Pursue a Pharmacological Approach?

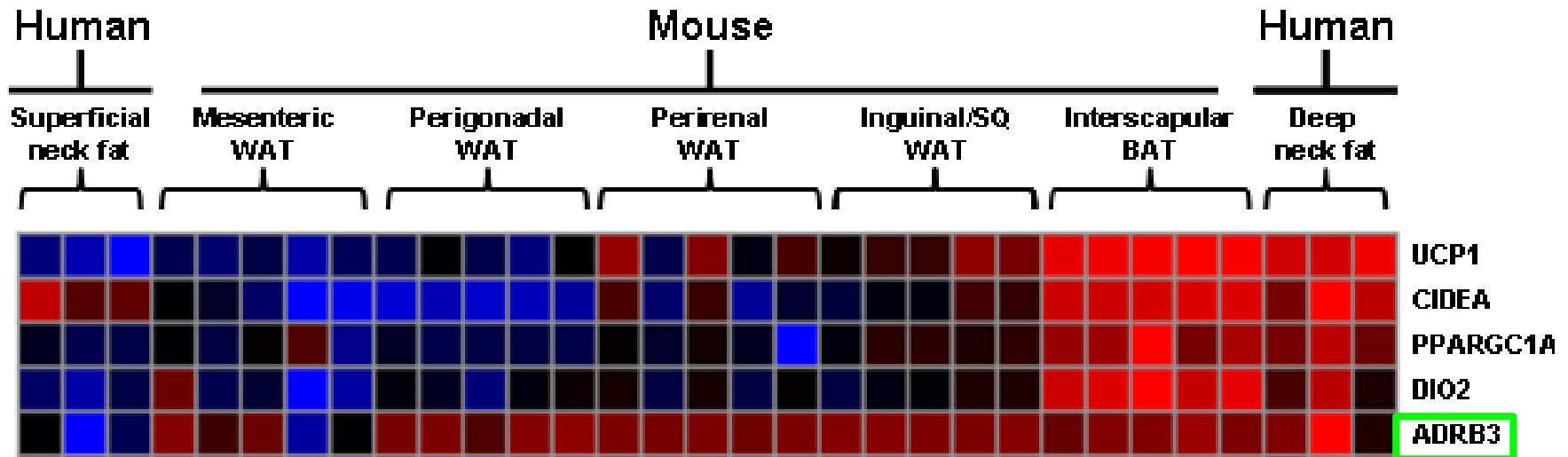
1. Potential for more specific targeting of human BAT.
2. Animal models show they are effective.
3. Likely greater adherence.
4. Combinations of approaches may be necessary.

The β_3 -AR is Expressed by Human BAT and WAT



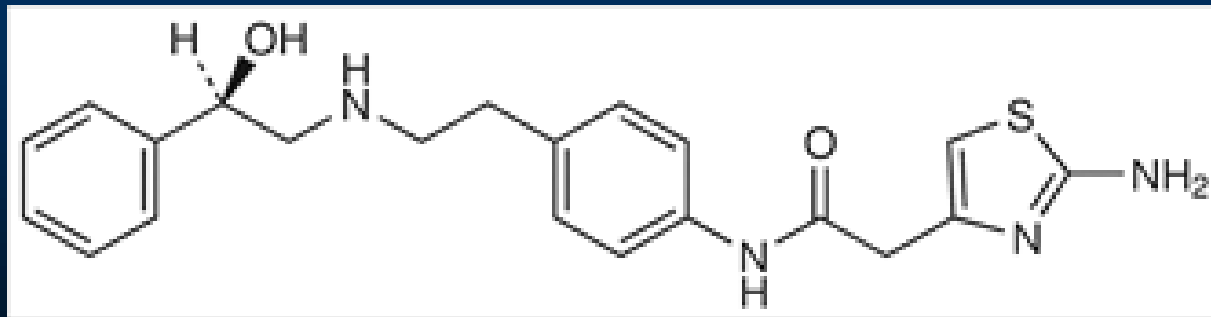
Virtanen KA, et al. NEJM 2009;360:1518

Yu-Hua Tseng, Andrew White



β 3-AR agonists can now be widely used in humans

- Over 45 million are affected by overactive bladder (OAB) in the US (c.f. 26 million with DM).
- Besides adipose tissue, there are β 3-AR's in the urinary bladder; activation relaxes the bladder.
- Mirabegron is a β 3-AR agonist approved by the FDA in 2012 for treatment of overactive bladder at 50 mg daily.



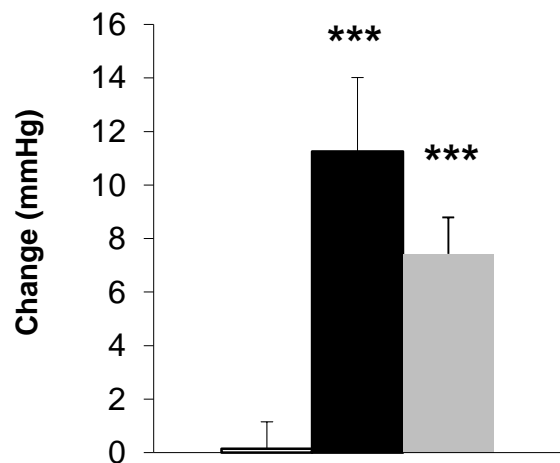
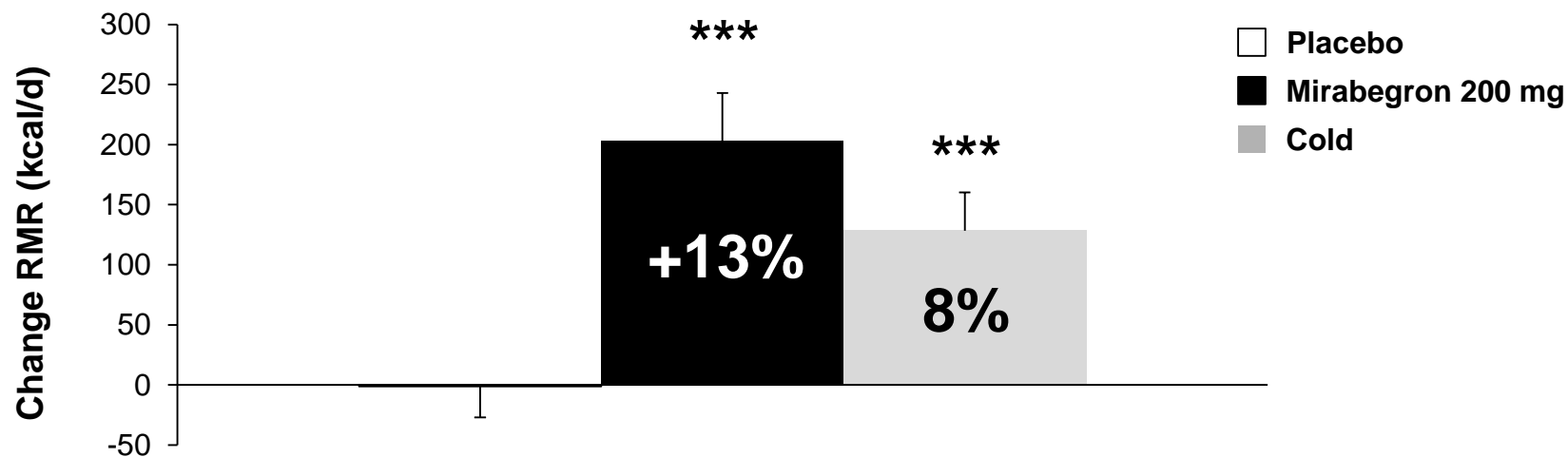
Proof-of-Concept Study Design

- Population: 12 young, lean, healthy men
- Each was treated acutely with placebo, mirabegron 200 mg, and exposed to mild cold (14 °C via vest / 20 °C room).
- Monitored vital signs, energy expenditure, drew blood prior to imaging, measured BAT metabolic activity via ^{18}F -FDG PET/CT.

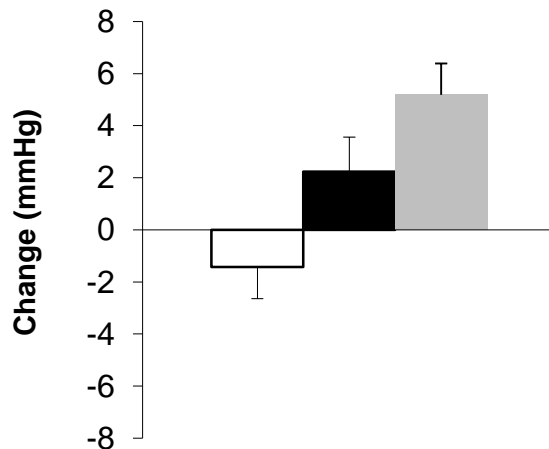


Lauren Weiner

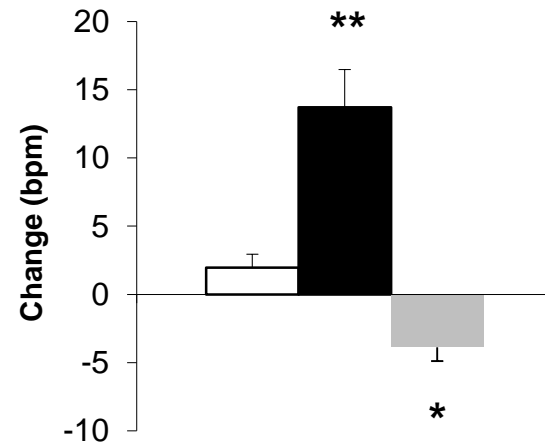
Mirabegron Agonist Increased Thermogenesis with Cardiovascular Stimulation



Systolic BP



Diastolic BP



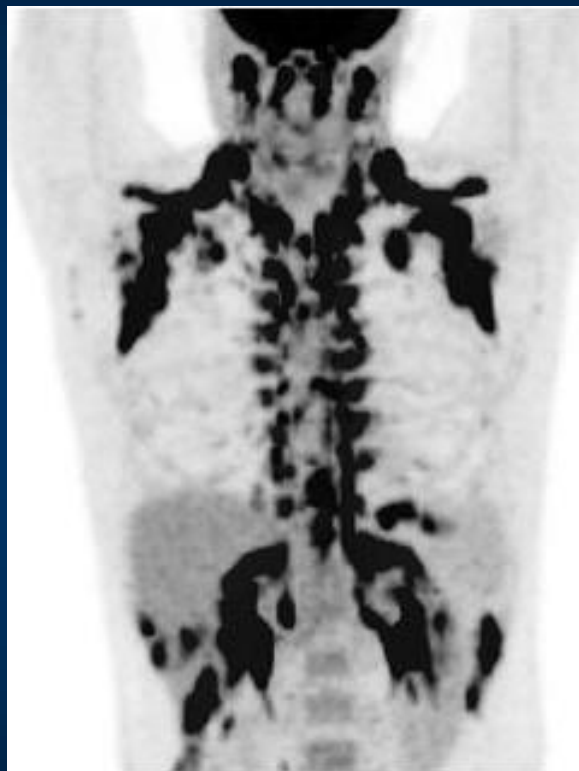
Heart Rate

The β 3-AR Agonist Activated Human BAT

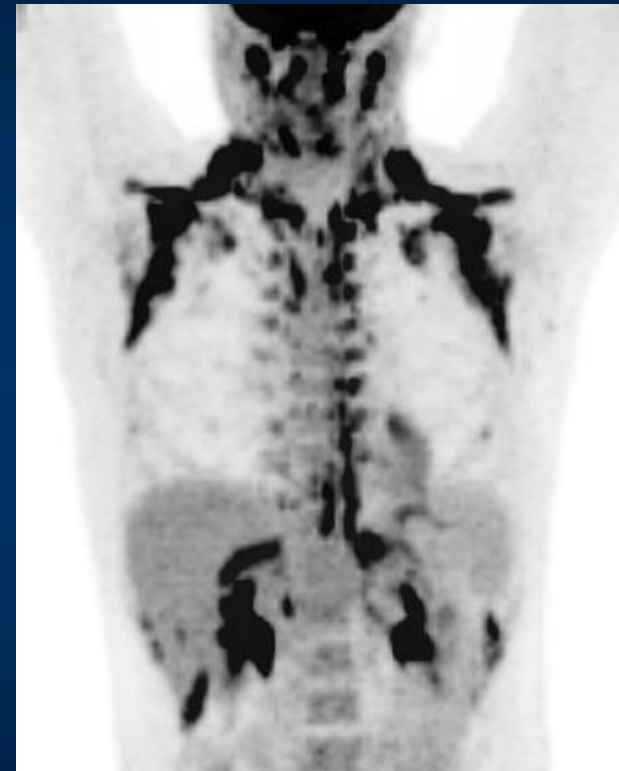
Placebo



Mirabegron



Cold



Final Summary

- **Brown adipocytes can be found in a substantial proportion of adult humans ($\leq 100\%$).**
- **Both cold and pharmacological activation of hBAT can substantially increase its mass and energy expenditure, but the extent is unknown.**
- **Brown fat may impact human metabolism at three different levels – energy balance, glucose metabolism, and hormonal regulation – with much to be learned.**
- **Coming up: “The Physiological Responses and Adaptation of Brown Adipose Tissue to Chronic Treatment with $\beta 3$ -Adrenergic Receptor Agonists.”**

Thank You

NIH



DEOB

Marc Reitman	Joyce Linderman
Monica Skarulis	Alison Baskin
Kong Chen	Cheryl Cero
Suzanne McGehee	Brooks Leitner
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